

AD_____

Award Number: W81XWH-05-1-0056

TITLE: Cancer Localization in the Prostate with F-18 Fluorocholine Positron Emission Tomography

PRINCIPAL INVESTIGATOR: Sandi Kwee, M.D.

CONTRACTING ORGANIZATION: The Queen's Medical Center
Honolulu, HI 98613-2413

REPORT DATE: January 2006

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.					
1. REPORT DATE (DD-MM-YYYY) 01-01-2006		2. REPORT TYPE Annual		3. DATES COVERED (From - To) 20 DEC 2004 - 19 DEC 2005	
4. TITLE AND SUBTITLE Cancer Localization in the Prostate with F-18 Fluorocholine Positron Emission Tomography				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-05-1-0056	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Sandi Kwee, M.D. E-mail: skwee@queens.org				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) The Queen's Medical Center Honolulu, HI 98613-2413				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT An imaging technique to identify the regions of cancer in the prostate gland could significantly enhance the diagnosis, treatment, and surveillance of this disease. This project evaluates fluorine-18 fluorocholine (F-18 FCH) positron emission tomography (PET) as a method for localizing cancer in the prostate gland. The research study plans to accrue 25 subjects who are undergoing radical prostatectomy surgery for prostate cancer. The subjects will undergo pre-operative PET scanning to acquire images of F-18 FCH uptake in anatomical sextants of the prostate. These results will be compared to the results of prostate biopsy and histopathologic analysis of the prostate specimen following surgery to determine the accuracy of F-18 FCH PET for detecting cancer in prostate sextants. The first major task of the project involved development of the human subjects research protocol and its approval by the institutional review board (IRB) at two medical institutions as well as the U.S. Army Human Subjects Research Review Board. Following completion of these tasks, subject recruitment was begun on July 18, 2005. As of December 20, 2005, ten subjects have participated in the research. Analysis of the preliminary data reveals that benign and malignant prostate sextants demonstrate statistically significant differences in F-18 FCH uptake as measured by PET. These preliminary findings concur with data obtained from a previous pilot study and supports potential diagnostic and therapeutic applications for this technique. Because the average tumor volume from the first 5 subjects was less than expected, a protocol change was submitted to the IRB in December 2005 to allow the inclusion of patients who may have higher tumor volumes. Project tasks that were assigned to the first project year have been completed in accordance to the Statement of Work (SOW). Completion of the remaining tasks is expected within the timeframe of the SOW.					
15. SUBJECT TERMS Prostate Cancer, Localization, Positron Emission Tomography, Fluorocholine					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT UU	18. NUMBER OF PAGES 18	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT U	b. ABSTRACT U	c. THIS PAGE U			19b. TELEPHONE NUMBER (include area code)

Table of Contents

Cover.....	1
SF 298.....	2
Introduction.....	4
Body.....	5-8
Key Research Accomplishments.....	8
Reportable Outcomes.....	8
Conclusions.....	9-10
References.....	11
Appendices.....	12-18

INTRODUCTION

Because choline metabolism is amplified in cancer, it may be possible to diagnose or detect cancer using a molecular imaging technique capable of measuring this biochemical pathway in vivo. One such technique, positron emission tomography (PET), can produce detailed whole-body images reflecting the cellular metabolism of the radioactive tracer F-18 fluorocholine (F-18 FCH), a synthetic analog of choline. The feasibility of using this technique to detect primary and metastatic disease has been demonstrated in patients with prostate cancer (1, 2). However, because PET is a metabolic imaging modality, it is not known whether this technique may only detect biologically aggressive tumors, or whether it may miss very small tumors because of metabolic activity from the surrounding normal tissues. The primary objective of this project is to estimate the accuracy of F-18 FCH PET for localizing malignant prostate tumors using the results obtained from step-section histopathology of prostatectomy specimens as the standard of reference. An important second objective of this study is to investigate F-18 FCH uptake in prostate tumors as a potential surrogate marker of tumor growth rate by correlating measurements obtained with PET to immunohistochemical markers of proliferation applied to prostatectomy specimens. Because the prevalence of prostate cancer is disproportionately higher than the mortality rate from this disease, there is a specific need for diagnostic techniques that can discriminate between rapidly progressive and indolent cancers, in order to identify the patients who will benefit most from aggressive treatment. An imaging technique capable of delineating and measuring the biological aggressiveness of malignant tumors in the prostate gland could significantly enhance the current medical armamentarium against prostate cancer, with novel applications relevant to the diagnosis, treatment, and surveillance of this disease.

BODY

SOW TASK 1: STUDY PREPARATION

Tasks 1a., 1b., and 1c., from the approved Statement of Work (SOW) were completed in the first year of the project. The following narrative describes the work performed in association with these tasks. A copy of the approved SOW is included in the appendix for reference.

Multi-Center Collaboration

This project and clinical study is a cooperative effort between The Armed Forces Institute of Pathology (AFIP), Tripler Army Medical Center (TAMC), and The Queen's Medical Center (QMC). Patients are recruited from the latter two medical centers to provide a broad sample of patients who qualify for the study and are candidates for the surgical treatment of prostate cancer. All medical imaging for the study is performed at QMC. Positron emission tomography (PET) with F-18 Fluorocholine (F-18 FCH) is an investigational imaging technique that is performed at QMC under an Investigational New Drug (IND) status with the Food and Drug Administration (FDA). An automated synthesis technique developed at QMC is used to produce the radiopharmaceutical F-18 FCH for clinical research (3). PET scanning is performed using a high-resolution research PET scanner (SHR-22000, Hamamatsu Photonics, KK). After surgery, prostate specimens are sent to the AFIP for detailed histopathologic and immunohistochemical analysis. Because the project requires significant cooperation and resource/effort sharing between institutions, a cooperative research and development agreement (CRADA) was signed between the Clinical Investigation Regulatory Office of the U.S. Army Medical Department Center and QMC on 6 July 2005, prior to initiating the clinical study component of the project.

Human Subjects Research Protocol

It was anticipated that patients recruited at TAMC could be serving as active duty personnel in the armed services. Design of the human subjects research protocol fittingly took into account both the protection of human subjects and military ethics. Separate principal investigators (PI) for QMC and TAMC were designated to provide fluency with the operations at each site, and to provide coordination with regards to the recruitment and referral of subjects. Separate medical monitors were also appointed at each institution to provide independent supervision of safety at each site. The final protocol required approval by the Institutional Review Board (IRB) at each institution, in addition to final review and approval by the U.S. Army Surgeon General's Human Subjects Research and Review Board (HSRRB). Because of the effort required in preparing the human subjects protocol, the Statement of Work (SOW) allocated the first 4 months of the project to finalizing and obtaining regulatory approval for the research protocol and study specific forms. The human subjects research protocol was reviewed by the HSRRB on 8 December 2004. Revisions to the protocol, consent form, and other documentation requested by the HSRRB were implemented and approved by the QMC IRB and TAMC IRB on 8 March 2005 and 14 April 2005, respectively. In March 2005, Dr. Kwee (project principal investigator (PI)) met with Dr. Sesterhenn (co-investigator) at AFIP to prepare the histopathologic analysis portion of the study protocol and to plan the logistics of the analysis. Notification of final protocol approval by the HSRRB was received on 3 May 2005. The completion of these activities fulfills the subtasks itemized under Task 1 of the approved SOW.

SOW TASK 2. SUBJECT RECRUITMENT AND DATA COLLECTION

Task 2, which was proposed to occur between months 4 and 20 of the project, is currently underway. Task 2 involves subject recruitment, imaging, pathology and data analysis.

Recruitment: From 1 August 2005 to 20 December 2005, ten subjects have been recruited to take part in the research study. For the first half of the recruitment period, recruitment was staggered so as to not enroll another subject until data analysis for the previous subjects was completed. Staggering was done to ensure that no unexpected problems occurred with specimen procurement and analysis. It was particularly important to confirm that specimens were procured, prepared, and shipped to AFIP without difficulty, since damage to the specimen could potentially result in the loss of clinically relevant data. After no difficulties were encountered, recruitment for the study was expanded in December 2005. In year two, there will be 8 months available to recruit 15 additional subjects. No difficulties are expected with accruing the total projected number of 25 subjects.

PET Scanning: At the time of this report, ten subjects have undergone F-18 FCH PET scanning of the prostate under the current research protocol. No significant problems have been encountered with PET scanning. For two subjects, PET scanning was not performed over the entire body because the subjects reported a history of claustrophobia. For these patients, PET scanning was limited to the pelvis and prostate gland. As required by the FDA, the PET imaging data that has been collected will be made available to the FDA and summarized in an IND Annual Report for F-18 FCH.

CT Scanning of the Prostate: As of 20 December 2005, ten subjects have undergone CT imaging of the pelvis under the study protocol using a conventional CT scanner (Picker Helical CT, Picker International, Cleveland, OH). CT was used to provide anatomical sextant correlation for the PET images. CT imaging was preferred over MRI of the prostate for several reasons. First, the CT procedure could be completed in little time (5 minutes versus 1 hour for prostate MRI) and on the same day as PET. Second, the radiology technologists assisting in the study were more familiar with performing CT of the pelvis, and data from the CT could be readily transferred to a radiation therapy planning workstation for future research on the use of CT and F-18 FCH PET to enhance prostate radiation therapy. Before initiation of the clinical protocol, a 3.0 T MRI scanner at QMC (Siemens Trio, Siemens) was evaluated by the PI for the project. It was found that the prostate MRI images obtained with an available external phased-array body coil were not as amenable as CT images to computer-aided image registration with PET. An endorectal MRI coil, which would have provided more detailed images of the prostate, was not yet available for this model of MRI scanner. The CT images have been registered to PET without difficulty using a commercial image registration software package (HERMES, Hermes Medical Solutions). All CT scans performed in this study have been clinically interpreted by a staff radiologist at QMC. No significant extraprostatic abnormalities have been found by CT in this study.

Pathology: Preliminary histopathologic data is available from the first 5 subjects enrolled. Data from more recently enrolled subjects remain at various stages of processing. These stages include surgery (scheduled up to 2 weeks after PET); fixation (5 days); shipping from Honolulu to AFIP (3 days); and histopathological analysis (1-3 weeks). Immunohistochemical analysis of the specimens will not be available for this interim report, since this activity is planned to occur in the second year of the project. Immunohistochemical analysis at one time will facilitate inter-subject comparisons and minimize the expense of this procedure. The available histopathologic data has been summarized by the PI in a scientific abstract which is included in appendix 2.

SOW TASK 3: DATA ANALYSIS

Task 3 of the SOW includes interim and final analysis of project relevant data. Preliminary results covering the first ten subjects is presented in this annual report. Results included in this interim analysis are summarized in a scientific abstract that has been submitted to the 2006 Annual Meeting of the Society of Nuclear Medicine (reproduced in Appendix 2). All PET images acquired to date have been evaluated and interpreted by Dr. Kwee and Dr. Coel. Interpretation was first performed independently and then jointly, to assess concordance. PET images were routinely registered to corresponding CT images of the pelvis prior to analysis. Region of interest analysis of the registered PET and CT images was performed to measure sextant regional prostatic F-18 FCH metabolism. Prostate images were acquired at two time points post-injection, based on new research findings by the PI supporting improved lesion detection with dual-time point PET imaging (1). Concordance between the two readers in identifying the prostate sextant with highest uptake was 100%. Sextant measures of F-18 FCH uptake were correlated with the histopathological results provided by the AFIP.

Based on the available histopathologic data, sextants with malignant involvement demonstrated significantly higher F-18 FCH uptake compared to benign sextants. On PET scanning ten minutes following F-18 FCH administration, the maximum standardized uptake value (SUVmax, a measure of the relative uptake of tracer within tissues) in malignant and benign sextants was 6.7 and 4.2, respectively. This difference in F-18 FCH uptake between malignant and benign sextants was statistically significant ($p = 0.0124$). On 1-hour delayed scanning, the difference in SUVmax in malignant vs. benign sextants was also statistically significant (6.2 vs. 3.7, $p = 0.0024$). These preliminary findings concur with findings from previous studies which compared F-18 FCH uptake in biopsy-defined benign and malignant prostate sextants (1, 2). Step-section prostate histopathology has provided this project a gold-standard reference for estimating the accuracy of PET. Based on the available histopathologic data from 5 subjects from this study and 7 subjects from a pilot study, the sensitivity and specificity of F-18 FCH PET for sextant localization was calculated to be 80% and 70% respectively. While additional data is necessary to strengthen the certainty of these estimates, the findings are promising and appear comparable to recently reported measures of the accuracy of endorectal MRI/spectroscopy for cancer detection in the prostate (4).

Preliminary review of the clinical and histopathologic data suggest that subjects recruited from TAMC have a lower disease burden compared to subjects recruited from the Hawaiian community. The average total tumor volume by step-section analysis of specimens from TAMC was 3.7 cc (range 0.03 cc to 5.7 cc), which is significantly lower than the average tumor volume of 8.3 cc (range 0.2 cc to 28.7 cc) from prostates obtained from subjects recruited from the community (1). The average mass of prostate specimens from TAMC was also significantly less than those from a previous study of patients at QMC (average mass, 48 g vs. 62 g). These differences are likely due to differences in the prevalence of screening (disease detection), racial/ethnic distribution, as well as patient/physician preferences for treatment (surgery vs. radiation) between TAMC and QMC. Furthermore, the current mean age of subjects referred from TAMC is 58 years (range 47-63), which is significantly lower than the mean age of subjects from our pilot study at QMC (67 years, range 38-83) ($p < 0.05$). It is not surprising that younger patients (who have also been screened for prostate cancer) have lower volumes of disease.

However, one potential extrinsic factor to account for an apparently lower volume of disease in recruited subjects is the use of clinical study participation criteria that may have the un-planned effect of excluding patients with higher disease burdens. Specifically, inclusion/exclusion criteria in the current study protocol excludes patients if greater than two-thirds of their biopsy specimens contain malignancy. While this criterium was originally conceived to ensure an adequate proportion

of benign and malignant sextants for analysis, it may have led to the unintended exclusion of patients with higher disease burdens. While it is important to study patients with low volumes of prostate cancer to estimate the size-threshold for detecting malignant tumors with F-18 FCH PET, the inclusion of a disproportionate number of patients with very small tumors (or even microscopic tumors) may produce an unreasonable negative impact on accuracy estimates (ie. sensitivity, specificity) for detecting prostate malignancy with F-18 FCH PET. Given that the resolution of PET scanning is between 0.4 and 0.8 cm, it is not expected that very small lesions will be detected by this modality. It is worth noting that many small tumors are also of minor clinical importance, since they would have likely remained confined (ie. hidden) in the prostate for the duration of a patient's lifetime (5). Therefore, this study should include patients with higher tumor volumes in order to appropriately answer the question of whether clinically significant cancers can be detected with PET. To this end, a protocol change removing the inclusion criteria limit on biopsy tumor volume has recently been submitted for expedited IRB review in December 2005. The change has been preliminarily approved by local IRBs and will be submitted for HSRRB approval prior to implementation. This protocol modification will not alter the tasks described in the SOW. No changes to the original approved SOW are recommended or requested.

SOW Task 4: FINALIZE PROPOSED ANALYSIS AND DESIGN SECONDARY STUDIES

Task 4, which includes final data analysis, manuscript preparation, and design of subsequent studies, is scheduled to occur during the last four months of the second year of the project. These activities are not covered in this annual report for the first project year.

KEY RESEARCH ACCOMPLISHMENTS

Preliminary analysis based on histopathologic correlation data from 11 subjects supports the accuracy of F-18 FCH PET for localizing cancer to prostate sextants. In all subjects, the prostate sextant associated with the highest degree of F-18 FCH uptake demonstrated carcinoma on histopathologic analysis.

REPORTABLE OUTCOMES

- Data derived from this study was included in an FDA Annual Report supporting Investigational New Drug Application #66,319 (18F-Fluorocholine) submitted on 15 December 2005.
- A research grant proposal entitled "Image-directed Treatment of Prostate Cancer Using Positron Emission Tomography To Assess Tumor Proliferation and Repopulation" has been submitted to the Prostate Cancer Foundation on 1 December 2005. Preliminary data from this current project was used to support the research proposal.
- An abstract reporting key research accomplishments from the first year of this project was submitted for presentation at the 53rd Annual Meeting of the Society of Nuclear Medicine.

CONCLUSION

This interim report provides a preliminary estimate of the diagnostic accuracy of F-18 FCH PET for detecting cancer in prostate gland sextants. A gold-standard form of histopathologic diagnosis was used as the reference for these accuracy measures. Based on histopathologic correlation with 11 completely embedded whole-mounted prostate specimens, the sensitivity and specificity of F-18 FCH PET for the detection of cancer in prostate sextants is estimated at 80% and 70%, respectively. These preliminary results are based on available data in a limited number of subjects. This level of accuracy appears comparable to reported measures of localization accuracy for magnetic resonance imaging/spectroscopy of the prostate (4).

As discussed in the body of this report, the volume of malignant tumor found in several of the collected specimens was relatively small. The total combined tumor volumes in 4 of 5 analyzed specimens was less than 5 cc. Not unexpectedly, individual small and microscopic tumors may not produce a sufficiently abnormal signal on PET to allow for their detection. Nevertheless, in all the specimens collected thus far, the prostate sextant exhibiting the highest level of F-18 FCH activity has demonstrated carcinoma on analysis of the whole-mounted specimen. Such information pointing to the location of the most abnormal zone of the prostate may prove helpful to guide prostate biopsy or focus the area of treatment. For example, if the most abnormal areas of the prostate seen on F-18 FCH PET are targeted to receive treatments at a higher dose, then there will be greater certainty that areas of malignancy will be sterilized while reducing the potential for damage to nearby normal structures. Potential treatment methods which may be enhanced by image-guidance using F-18 FCH PET include focal ablative therapies such as cryoablation (an FDA approved treatment for cancer confined to the prostate) and radiation therapy with dose augmentation to single or multiple dominant tumor lesions. In the latter instance, by delivering higher doses of radiation to dominant areas of malignancy while treating the remainder of the prostate gland with a safer dose of radiation, both the therapeutic efficacy and safety of the treatment could be improved. Currently, there are no widely available techniques to provide cancer-targeted image-guidance in conjunction with these treatments. And for diagnosis, needle biopsies of the prostate could be directed to the areas that appear most abnormal on PET, potentially increasing the detection rate of biopsy while sparing patients the discomfort and complications of multiple biopsies. If prostate PET imaging with F-18 FCH is shown to have reasonable accuracy for detecting prostate cancer, it will be appropriate to explore the feasibility of these imaging-enhanced diagnostic and therapeutic procedures.

With regards to using an imaging technique such as 18F-FCH PET for population-based prostate cancer screening, it seems unlikely that PET, or any other non-invasive imaging technique, will be capable of detecting all malignant prostate tumors, especially those which are very small. Given that the current study involves only patients who have been previously diagnosed with prostate cancer, the results from this study cannot directly address the issue of screening. With regards to screening, one must consider the likelihood that very small tumors, especially in patients with a limited life-expectancy, may never grow to the point of causing clinical symptoms or death. Therefore, rather than attempt to identify all patients with cancer, an alternative screening objective may be to identify specifically those patients who are at risk of *suffering* from prostate cancer (eg. those with rapidly growing tumors). Since the prevalence of prostate cancer is much greater than the mortality rate of this disease, the optimal cost-effective national strategy for screening prostate cancer may involve selectively identifying patients with biologically aggressive tumors. Because F-18 FCH PET is a metabolic imaging modality, it may be possible to selectively detect biologically aggressive tumors with this technique, provided that the amount of choline used by cells may be a reflection of their proliferative activity. In this regard, the accrual of more patients in the second year of this project is important in that it will allow us to study the correlation between F-18 FCH

accumulation in the prostate and available histopathologic measures of cancer aggressiveness (Gleason Score, MIB-1 immunohistochemical staining) applied to the prostate specimen. Until more specimens are acquired, it will not be possible to make statistically valid comparisons using these histopathologic measures.

The patients recruited to this study are assumed to be at low risk for advanced metastatic prostate cancer based on accepted clinical criteria. In higher risk patients, we have been accumulating data which supports whole-body prostate cancer staging with F-18 FCH PET. PET distinguishes itself from most other radiological imaging modalities in that it provides an extensive survey of the body in one session. Using F-18 FCH PET, we have found it possible to detect cancer spreading to areas beyond the prostate such as the lymph nodes and distant skeletal sites (2). Because both prostate and whole-body PET images are obtained from patients enrolled in the current study, data from this project can eventually serve as a reference for comparisons with patients who have metastatic cancer. Therefore, this project will be contributing to future studies of whole-body cancer staging with 18F-FCH PET. Completion of the tasks remaining for year two will determine the feasibility of these promising and novel clinical applications for 18F-FCH PET.

REFERENCES

1. Kwee SA, Wei H, Yun D, Sesterhenn I, Coel MN. Localization of Primary Prostate Cancer with Dual-phase 18F-Fluorocholine PET. *Journal of Nuclear Medicine*. 2006:Accepted for Publication.
2. Kwee SA, Coel MN, Lim J, Ko JP. Prostate cancer localization with 18fluorine fluorocholine positron emission tomography. *J Urol*. 2005;173(1):252-255.
3. Lim J, Dorman E, Cabral C. Automated Production of [18F]FECh and [18F]FCH: Preparation and Use of [18F]Fluoroalkane Sulfonates and Fluoroalkylation Agents. *J. Label Compd Radiopharm*. 2003;46(S1):S403.
4. Mullerad M, et al. Comparison of endorectal magnetic resonance imaging, guided prostate biopsy and digital rectal examination in the preoperative anatomical localization of prostate cancer. *J Urol*. 2005;174(6):2158-2163.
5. Konety BR, Bird VY, Deorah S, Dahmouch L. Comparison of the incidence of latent prostate cancer detected at autopsy before and after the prostate specific antigen era. *J Urol*. 2005;174(5):1785-1788; discussion 1788.

APPENDIX 1: Approved Statement of Work**Cancer Localization in the Prostate with F-18 Fluorocholine Positron Emission Tomography****Task 1. Study Preparation, Months 1-4:**

- a. Finalize research protocol and study-specific forms.
- b. Obtain institutional review board (IRB) approval of study protocol and consent form at project sites: Tripler Army Medical Center (TAMC), Queen's Medical Center (QMC), and the Armed Forces Institute of Pathology (AFIP).
- c. Orient all study personnel on protocol and methods.

Task 2. Subject Recruitment and Data Collection, Months 4-20:

- a. Begin subject recruitment at TAMC and QMC. A total of 25 subjects will be recruited from both sites over a 16 month period.
- b. Subjects will undergo whole-body F-18 FCH PET scanning at QMC to acquire images of the prostate gland.
- c. Subjects will undergo a CT or MRI scan of the prostate at QMC.
- d. Following surgery, the prostatectomy specimens will be delivered to AFIP for processing and analysis. Analysis procedures include surgical histopathology and immunohistochemical staining for the Ki-67 antigen. The data will be recorded on study-specific pathology forms.
- e. All data will be entered into a study database for analysis.

Task 3. Data Analyses, Months 6 – 20:

- a. PET image analysis will be performed at QMC by two physicians.
- b. Collected data will be analyzed and correlated in periodic interim analyses. Interim results will be summarized in annual reports.

Task 4. Final Analyses/Reporting and Design of Secondary Studies, Months 20-24:

- a. Finalize analysis of data and summarize results as stated in the specific aims.
- b. Prepare final report and manuscripts for publication.
- c. Design secondary studies using the collected data.

APPENDIX 2

Abstract Submitted to 53rd Annual Meeting of the Society of Nuclear Medicine
San Diego, CA
June 9-13 2006

(Attached on the following 2 pages)

Abstract/ Society of Nuclear Medicine 53rd Annual Meeting, June 3-7, San Diego, CA

TITLE: Cancer Localization in the Prostate with 18F-Fluorocholine PET: Initial Results From a Whole Prostate Histopathologic Correlation Study

ABSTRACT BODY:

Objectives: A method for localizing malignancy in the prostate gland may have clinical value as an adjunct for targeted biopsy or treatment. The objective of this preliminary histopathologic correlation study was to determine whether PET imaging with fluorine-18 fluorocholine (18F-FCH) can be used to localize malignancy in the prostate gland.

Methods: Histopathologic analysis was performed on completely embedded whole-mounted prostate specimens from eleven subjects who underwent whole-body PET imaging with 18F-FCH prior to radical prostatectomy. PET images of the prostate were acquired 10 minutes following intravenous administration of 3.3 to 4 Mbq/kg of 18F-FCH. The images were analyzed by region of interest analysis to measure the maximum standardized uptake value (SUVmax) corresponding to prostate sextants. These measures of uptake were correlated with the results of histopathology to determine the accuracy of 18F-FCH PET for detecting malignancy in prostate sextants.

Results: The average total tumor volume was 6.5 cc (range 0.5 cc to 28.7 cc). Forty of 60 prostate sextants contained at least one tumor on analysis of the whole-mounted specimen. The mean SUVmax in malignant sextants was significantly higher than in benign sextants (6.6 vs. 5.0 respectively, $p < 0.05$). In all patients, the sextant with the highest 18F-FCH uptake demonstrated carcinoma on analysis of the whole-mounted specimen. The area under the ROC curve for detecting malignant sextants on the basis of sextant SUVmax was 0.76. Using an SUVmax greater than 5.7 as the definition of malignant uptake, the sensitivity and specificity of 18F-FCH PET for sextant diagnosis were 80% and 70% respectively. Four of 8 false-negative sextants contained only tumors smaller than 0.5 cm in greatest dimension. No correlation between Gleason Score and SUVmax in malignant sextants was found in this limited series of patients.

Conclusions: PET imaging with 18F-FCH shows promise for identifying the dominant areas of malignancy within the prostate. However, small volumes of tumor may not be detectable on the basis of measured 18F-FCH uptake.

Research Support (if any): Congressionally Directed Medical Research Programs, Prostate Cancer Research Program

CONTROL ID: 234401

PRESENTER: Sandi Kwee

CONTACT PERSON INFORMATION: Sandi Alexander Kwee, 1301
Punchbowl St., Honolulu, HI, USA, 96813

AUTHORS (ALL): Kwee, Sandi Alexander¹; Thibault, Gregory ²; Stack,
Richard ²; Furusato, Bungo ³; Coel, Marc ¹; Sesterhenn, Isabell ³.

Institutional Author:

INSTITUTIONS (ALL): 1. Hamamatsu/ Queen's PET Imaging Center,
The Queen's Medical Center and University of Hawaii School of Medicine,
Honolulu, HI, USA.
2. Department of Urology, Tripler Army Medical Center, Tripler, HI, USA.
3. Department of Genitourinary Pathology, Armed Forces Institute of
Pathology, Washington, DC, USA.

Abstract Type: Phy/Sci/Pharm

TRACK: Oncology

CATEGORY: Oncology-Clinical Diagnosis

Considered for:

AWARDS:

PRESENTATION TYPE: Either Oral or Poster

KEYWORDS: Prostate Cancer, Positron Emission Tomography,
Fluorocholine.

Keyword Phrases: Tumor Localization

APPENDIX 3

Annual Report to The Food and Drug Administration

15 December 2005

IND#66319, Submission Serial # 007

Sponsor-Investigator: Marc N. Coel, MD

Prepared by:

Marc Coel, MD

Sandi Alexander Kwee, MD

Hamamatsu/ Queen's PET Imaging Center

1301 Punchbowl St.

Honolulu, HI 96813

Submitted to:

Food and Drug Administration

Center for Drug Evaluation and Research

Division of Medical Imaging and Radiopharmaceutical Drug Products

Attention: FDA – Document Room #8B-45

5600 Fishers Lane, HFD-160

Rockville, MD 20857

1. INDIVIDUAL STUDY INFORMATION:

1.1 Study Description:

Study Name: Human Biodistribution of F-18 Fluorocholine.

Institutional Study ID: RA-2003-02, approved by IRB on 5 February 2003.

Last renewal of this study was on 11/09/2005. Current expiration date is 31 October 2006. The study is on-going.

Institution: The Queen's Medical Center, Honolulu, HI

Purpose: To study the biological distribution and localization of F-18 fluorocholine using positron emission tomography in subjects with evidence of solid-organ malignancy or neurological disease (positive biopsy, imaging or serum marker result).

Study Name: Positron Emission Tomography of the Prostate.

Institutional Study ID: RA-2004-039, approved by IRB on 11 August 2004. This study was completed 31 July 2005.

Institution: The Queen's Medical Center, Honolulu, HI

Purpose: To develop image processing techniques that will facilitate correlation of PET images and optical images of prostate specimens after histologic sectioning.

Study Name: Cancer Localization in the Prostate with F-18 Fluorocholine

Positron Emission Tomography.

Institutional Study ID: RA-2004-040, approved by IRB on 9 February 2005.
Current Expiration date is 24 October 2006.

Institution: The Queen's Medical Center, Honolulu, HI

Purpose: To correlate F-18 Fluorocholine PET images of the prostate with detailed histopathologic analysis of the prostate gland after it is obtained following radical prostatectomy.

1.2 Subject Information:

Total Planned for Inclusion: 180

Number of Subjects Entered to Date: 117 (as of December 2, 2005)

Number of Subjects Completed Participation: 117

Number of Subjects Who Dropped Out of the Study: 0

Table 1: Recruited subjects, tabulated by age, gender, and racial category

	Number
Age:	
21-30	3
31-40	4
41-50	10
51-60	17
61-70	39
71-80	30
81-90	14
Gender:	
Male	104
Female	13
Racial Categories:	
American Indian/ Alaskan Native	0
Asian	70
Native Hawaiian/ Other Pacific Islander	0
Black or African American	2
White	42
More than one race:	3

1.3 Available Results:

A paper published in the Journal of Nuclear Medicine is appended to this report.

2. SUMMARY INFORMATION:

2.1 Summary of Adverse Experiences:

There were no adverse experiences associated with the use of F-18 fluorocholine noted during this period.

2.2 Summary of Safety Reports:

No IND Safety Reports were submitted during this period.

2.3 List of Deaths:

No subjects died during participation in the investigation.

2.4 Withdrawals Due to Adverse Experiences:

No subjects withdrew because of an adverse experience.

2.5 Information gained about drug's actions:

Not applicable.

2.6 Preclinical Studies:

None performed.

2.7 Manufacturing or microbiological changes:

No new manufacturing or microbiological changes since previous annual report.

3. INVESTIGATIONAL PLAN FOR 2005:

1) Continue current protocol described in Section 1.1.

2) Collected data is currently being analyzed to determine the feasibility of breast cancer detection/localization using F-18 fluorocholine PET. Given that the majority of subjects accrued in this investigation have been male, an investigation of breast cancer localization would provided additional data on F-18 FCH biodistribution in premenopausal and postmenopausal females. Under the current protocol, female subjects must have documentation of non-pregnant status or the inability to become pregnant. This documentation must be obtained through medical history or laboratory testing.

4. INVESTIGATIONAL BROCHURE REVISIONS:

The investigators have received a complete copy of the investigational plan and research protocols.

5. PHASE 1 PROTOCOL REVISIONS

None.

6. FOREIGN MARKETING DEVELOPMENTS:

None.

7. LOG OF OUTSTANDING BUSINESS:

None.

8. REFERENCES:

None.